REMARKS

Claims 1-26 and 44-47 are pending in this application. Claims 27-43 have been canceled without prejudice or disclaimer. Claim 4 has been amended.

Applicants, by canceling or amending any claims, make no admission as to the validity of any rejection made by the Examiner against any of these claims. Applicants reserve the right to reassert any of the claims canceled herein or the original claim scope of any claim amended herein, in a continuing application.

Claim 4 has been amended to correct a grammatical error. Amended claim 4 recites "…wherein the inner surfaces of the plates are parallel to side walls of the container." Support for this amendment can be found throughout the claims and specification as originally filed.

No new matter has been added.

In view of the remarks set forth below, further and favorable consideration is respectfully requested.

I. At page 2 of the Official Action, claim 4 is objected to.

The Examiner requests that claim 4 be amended to correct a grammatical error. Applicants respectfully submit that claim 4 has been amended as suggested by the Examiner. Accordingly, reconsideration and withdrawal of this objection is respectfully requested.

II. At page 2 of the Official Action, claims 1-26, 44, 45 and 47 have been rejected under 35 USC § 103(a) as being unpatentable over Arav (US Patent No. 5,873,254) in view of Polk (US Patent No. 3,074,247).

The Examiner asserts that it would have been obvious to modify the apparatus described by Arav with the passage and container thickness described by Polk to obtain the claimed subject matter.

In view of the remarks set forth herein, this rejection is respectfully traversed.

To establish a *prima facie* case of obviousness, the Examiner must satisfy three requirements. First, as the U.S. Supreme Court held in *KSR International Co. v. Teleflex Inc.,* 550 U.S. 398 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, 550 U.S. 398 at 417.) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must

teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

Regarding motivation to modify properly combined references, **MPEP 2143** states that where the prior art conflicts, all teachings must be considered and that the fact that references can be combined or modified is not sufficient to establish *prima facie* obviousness. **MPEP 2143** further states that there must be some suggestion or motivation to modify the references, and there must be a reasonable expectation of success.

MPEP 2143.01 states that a proposed modification cannot render the prior art unsatisfactory for its intended purpose. If it does, then there is no suggestion or motivation to make the proposed modification. Further, the proposed modification cannot change the principle operation of a reference.

It is submitted that a *prima facie* case of obviousness has not been established for at least the reason that there is no motivation to modify the cited references to arrive at the presently claimed subject matter. In particular, Applicants submit that the proposed modification, i.e., utilizing the passage and container thickness described by Polk in the device described by Arav et al., would change the principle of operation of the device described in Arav et al., i.e., multigradient directional freezing. In addition, Applicants submit that Arav et al. expressly teaches away from the conventional freezing method described by Polk.

Independent claim 1 is directed to an apparatus for freezing a biological sample in a flexible container, the apparatus comprising: a cooling axis; at least one set of two cooling plates with inner surfaces positioned along the cooling axis, each at least one

set of two cooling plates comprising a first longitudinal plate dimension perpendicular to the cooling axis, and a second horizontal plate dimension parallel to the cooling axis; a passage defined between the inner surfaces of the plates, the passage comprising an inner width that conforms to an outer width of the container, and a height no larger than the first longitudinal plate dimension; and a motion unit adapted to move the container through the passage along the cooling axis such that the sample is cooled by conduction from direct contact between the container and the inner surfaces of the plates. Claims 2-26, 45, 46 and 47 each depend, either directly or indirectly, from claim 1.

In contrast to the presently claimed subject matter Arav is directed to device having a laterally varying thermal gradient and a mechanism for moving the sample along the thermal gradient at a controlled velocity. *See* Arav at the abstract.

Polk is directed to a conventional freezing apparatus which aims to reduce frosting during loading and removal of packages vertically disposed between cooling plates. ***According to Polk, the packages, once in place, remain static at their position***.

Applicants submit that there is no motivation to modify the device described by Arav with the teachings of Polk for at least the reason that doing so would destroy the principle mode of operation of Arav, i.e., the movement of the sample along a temperature gradient. In this regard, Applicants note that the device of Arav requires movement to apply directional freezing onto the sample so as to allow controlled nucleation or seeding. Modifying the device of Arav to cool a container in a fixed

position at an essentially fixed temperature, as required by Polk, would destroy its principle of operation and result in destruction of cells, as further discussed below.

As provided at column 1, lines 40-50 of Arav:

> The conventional method for freezing biological samples is to place them in a chamber and lower the temperature of the chamber in a controlled manner. Samples frozen in this manner freeze from the outside in. The thermal gradient within the sample is determined implicitly by the temperature of the chamber and the thermal conductivities of the materials within the sample, and is not explicitly controllable. This makes it difficult to achieve the optimal cooling rate, which minimizes both the toxicity associated with cooling too slowly and the mechanical damage associated with cooling too fast.

However, in order to overcome these deficiencies, Arav utilize multigradient directional freezing. In particular, the device and method described by Arav utilizes "a laterally variable temperature gradient" that is disposed along a track upon which a sample travels to achieve controlled nucleation. In particular, at column 5, lines 8-42, Arav indicates that:

> The device of the present invention enables the implementation of controlled seeding in the freezing of biological samples. When any liquid is cooled below its freezing point, it remains a liquid, in an unstable supercooled state, for at least a short time. Freezing starts at nucleation sites that are distributed substantially randomly throughout the volume of the liquid, and spreads through the rest of the liquid. In the conventional, equiaxial (nondirectional) method of freezing biological samples, ice grows with uncontrolled velocity and morphology, and may disrupt and kill the cells of the samples.
>
> Directional freezing allows controlled nucleation, or seeding, of freezing, at least in principle. As a straw containing a biological sample is moved forward along a thermal gradient, from a temperature above the freezing point of the sample to a temperature below the freezing point of the sample, at some point in time, the leading edge of the straw reaches a point in space at which the temperature is below the freezing point of the sample. The leading end of the straw is now frozen, for example by touching it with a cold object such as a small amount of liquid nitrogen. Uncontrolled freezing proceeds backwards along the straw to the point in space at which the temperature is equal to the freezing point of the

> sample. As the straw continues to move forward, the frozen part of the sample nucleates freezing of the liquid part of the sample as the liquid part of the sample passes the point in space at which the temperature is equal to the freezing point of the sample. Thus, uncontrolled freezing, with consequent random destruction of cells, is confined to a small region at the leading end of the straw, and controlled freezing occurs at a freezing front that moves backwards along the straw but remains substantially stationary with respect to the thermal gradient, substantially at the point along the thermal gradient at which the temperature is equal to the freezing point of the sample.

In complete contradiction with Arav, Applicants submit that ***the device and methods described by Polk provide an essentially constant freezing rate at all times***. In this regard, according to column 2, lines 12 to 24:

> During the preceding operations and somewhat prior thereto, liquid refrigerant R is admitted to the plates at a metered or controlled rate of flow such that the level of refrigerant in the plates rises to about the height of the first tier of packages at about the time that the first tier is placed in position. **The plates then remain in contact with the sides of the first tier of packages (FIG. 3) for a given period of time, namely, the cycling rate of the machine which would be the total time required to freeze the content of the package** divided by the number of rows of the packages, after wichic the plates are moved away from the packages and a second row admitted… (Emphasis added).

In this regard, also according to column 2, lines 34 to 43:

> During the time period of admittance of tiers of packages periodically, the refrigerant is metered or supplied to the plates at a controlled rate so that the buildup of refrigerant in the plats is commensurate with the rise of the tiers of packages in the space between the plates. The flow of refrigerant cannot necessarily be at a constant rate, since the evaporation of the refrigerant will presumably take place at a greater rate as additional packages are added to result in increased heat transfer.

In other words, Polk requires that the plates with the packages until freezing of the content of the packages and refrigerant is replaced between rows in order to maintain a single, constant rate of cooling for all packages. Therefore, Applicants submit that Polk does not operate with a temperature gradient, but rather with a fixed temperature in

order to avoid frosting caused by changing temperatures. Applicants once again note that that Arav teaches away from this principle, because Arav requires a temperature gradient which a sample moves through.

Further, Applicants submit according to Polk, when operable, i.e., for cooling, the packages in a row must be in a fixed position directly against the surface of the cooling plates. Any disruption in the contact between the packages and the plates will result in an undefined loss and/or addition of cooling. Applicants note that ***this is not a temperature gradient*** within the meaning of the present application or of Arav.

In view of the express contradictory teachings of both Arav and Polk, Applicants respectfully disagree with the Examiner's position that modifying the directional freezing device described by Arav, with a device that cools by a conventional method, would not destroy the principle mode of operation of Arav. In this regard, Applicants note that at page 13 of the Official Action the Examiner asserts that:

> Arav utilizes directional freezing and implements temperature gradients within cooling plates to allow for controlled nucleation. The introduction of freezing using conduction will not destroy the operation of Arav, as temperature gradients will still occur within the cooling plates so that directional freezing and controlled nucleation can occur.

However, Applicants submit that, as clarified herein, the introduction of conventional freezing with a constant temperature, as described by Polk would destroy the principle of operation described by Arav. Accordingly there is no motivation to modify Arav, as suggested in the Official Action, to achieve the presently claimed subject matter.

With specific regard to the modification proposed by the Examiner, Applicants submit that modifying Arav to have direct contact with the cooling blocks in a fixed

position, as required by Polk, would destroy the controlled temperature gradient that Arav utilizes. On the other hand, if the sample is moveable along the gradient as proposed by Arav, ***cooling by fixed direct contact cannot occur***, which as discussed above is the mechanism by which Polk operates. Accordingly, there is no motivation to modify Arav with Polk to achieve the claimed subject matter.

Applicants additionally note that, at column 2, lines 3-11, Polk clearly indicates that in order to move the sample, the cooling blocks must be separated from the package. Applicants submit that if, in fact, the cooling blocks are separated from the sample to allow for movement, the proposed modification of Arav with Polk cannot result in the claimed subject matter because the sample will not be "cooled by conduction from ***direct contact*** between the container and the inner surfaces of the plates," as recited in claim 1.

In view of the foregoing, Applicants submit that, for at least the reason that substituting directional freezing with conventional freezing will destroy the principle mode of operation of Arav, there is no motivation to modify Arav with the device and methods described by Polk.

In addition to lacking motivation to modify Arav with the teachings of Polk, Applicants submit that Arav teaches away from the conventional freezing described by Polk. As discussed above, Applicants once again refer the Examiner to Arav, for example, at column 1, lines 40-50 and column 5, lines 8-42, as well as the contradictory teachings in Polk, for example, at column 2, lines 3-11 and 38-43. Since the express statements in Arav would lead a skilled artisan in a direction opposite of that taken in Polk, and vice versa, Applicants submit that Arav teaches away from Polk.

In view of the foregoing, Applicants submit that none of the cited references, render the presently claimed subject matter obvious, within the meaning of 35 USC § 103(a) Thus, the Examiner is respectfully requested to withdraw this rejection of claims 1-26, 44, 45 and 47.

III. At page 11 of the Official Action, claim 46 has been rejected under 35 USC § 103(a) as being unpatentable over Arav (US Patent No. 5,873,254) in view of Polk (US Patent No. 3,074,247) and Eck et al. (DE PublicationNo. 10056181 C1).

The Examiner asserts that claim 46 is obvious for the reasons set forth in the Official Action.

In view of the following this rejection is respectfully traversed.

The presently claimed subject matter, Arav and Polk are each discussed in detail above. Applicants submit that there is no motivation to modify the methods and device of Arav with the teachings of Polk for the reasons set forth above. Further, Applicants submit that Arav expressly teaches away from the methods employed by Polk. Eck et al. do not remedy the deficiencies of the combination of Arav end Polk because, Eck et al. do not provide any teaching or suggestion to reconcile the contradictions in Arav and Polk.

In addition, Applicants submit that submit that neither the combination of Arav and Eck et al. nor Polk et al. teach or suggest every element of the claimed subject matter. In this regard, Applicants note that Polk merely describes a cartridge for freezing a sample.

In view of the foregoing, Applicants submit that none of the cited references, render the presently claimed subject matter obvious, within the meaning of 35 USC § 103(a) Thus, the Examiner is respectfully requested to withdraw this rejection.

CONCLUSION

In view of the foregoing, Applicants submit that the application is in condition for immediate allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

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